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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,101	12/30/2005	Akira Kato	0425-1236PUS1	6760

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EXAMINER	
SOROUSH, ALI	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
07/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,101	KATO ET AL.	
	Examiner	Art Unit	
	ALI SOROUSH	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's response filed on 06/18/2008 to the Office Action mailed on 06/04/2008 is acknowledged.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-17 and 23-25) in the reply filed on 06/18/2008 is acknowledged.

Status of the Claims

No claim amendments were submitted with the aforementioned response. Therefore, claims 18-22 are withdrawn as being drawn to non-elected subject matter and claims 1-17 and 23-25 are currently pending examination for patentability.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 7, 15, 16, and 24 recite "good solvents" and "poor solvents", however it is not clear from the claims or the specification what would constitute a "good solvent" and would constitute a "poor solvent". Therefore, these terms are indefinite and fail provide the meets and bounds of the aforementioned solvents.

Claim 25 provides for the use of a high-pressure homogenizer, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 25 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5, 7-11, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sjostrom et al. (International Application Published Under the PCT WO 90/15593, Published 12/27/1990).

Sjostrom et al. teach, "A process for the preparation of submicron size, monodisperse drug-particles of a drug of low water solubility by emulsifying an organic solution of the drug in an aqueous phase and then removing the organic solvent resulting in drug precipitation, containing the steps: a) emulsifying the organic solution in the presence of an emulsifier comprising a surfactant capable of adsorption on the surface of a precipitated drug-particle; b) removing the organic solvent from suspension; and d) recovering the precipitated drug-particles from the aqueous phase or storing the same in the original aqueous phase." (See abstract). "Removal of the organic solvent from the suspension can take place in different ways." (See page 2, Lines 28-29). In a preferred embodiment, "[a]n emulsion of cholesteryl acetate dissolved in toluene and an aqeous phase containing ethoxylated nonylphenol ether as a surfactant is prepared in the following manner. The drug substance, cholesteryl acetate, is dissolved in toluene. The solution is emulsified with an aqueous phase containing ethoxylated nonylphenol ether as a surfactant to form an oil-in-water type emulsion." (See page 9, Lines 17-23). "The oil/water phase ratio is 10/90, and the amount of surfactant is 5% by weight based on the weight of the oil phase." (See page 10, Lines 18-20). "[T]he emulsions were prepared by homogenization with a microfluidizer, and the particles were measured by quasi-elastic light scattering." (See page 10, Lines 6-8). "The organic solvent, toluene, is then evaporated from the emulsion, whereby the drug model substance precipitates and the crystals are stabilized by the surfactant, said surfactant being adsorbed on the surface of the precipitated particles." (See page 9, Lines 24-28). "The particle size in the suspension lies within the range of between 80 nm and about 400 nm." (See page 10, Lines 24-25). For the foregoing reasons the instant method is anticipated.

Claims 1, 3-6, 9, 11, 12, 15, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Chaubal et al. (US Patent Application 2004/0245662, Published 12/09/2004, Filed 11/07/2003).

Chaubal et al. teach, a "[m]ethod for preparing submicron particles of antineoplastic agents." (See title). "The particles generally produced have an average particle size of less than about 1000 nm and are not rapidly soluble." (See abstract). "Preferably the organic compound or the pharmaceutically active compound is poorly water-soluble. What is meant by 'poorly water soluble' is a solubility of the compound in water of less than about 10 mg/ml, and preferably less than 1 mg/ml." (See paragraph 0046). "The process for preparing the particles can be separated into four general categories. Each of the categories of processes share the steps of: (1) dissolving an organic compound in a water miscible first solvent to create a first solution, (2) mixing the first solution with a second solvent of water to precipitate the organic compound to create a pre-suspension, and (3) adding energy to the pre-suspension in the form of high-shear mixing or heat, or a combination of both, to provide a stable form of the organic compound having the desired size ranges defined above. The mixing steps and adding energy step can be carried out in consecutive steps or simultaneously." (See paragraph 0053). "The energy-addition step involves adding energy through sonication, homogenization, countercurrent flow homogenization, microfluidization, or other methods of providing impact, shear or cavitation forces ... In one preferred form of the invention, the energy addition step is effected by a piston gap homogenizer such as one sold by Avestin Inc. under the product designation EmulsiFlex-C160." (See paragraph 0077). In a preferred embodiment, "2.08 g of carbamazepine was dissolved into 10 mL of NMP [N-methyl-2-pyrrolidinone] . 1.0 mL of this concentrate was subsequently dripped

at 0.1 ml/min into 20 ml of a stirred solution of 1.2% lecithin and 2.25% glycerin ... The predispersion was next homogenized cold ... for 35 minutes at 15,000 psi. The pressure was increased to 23,000 psi and homogenization was continued for another 20 minutes." (See paragraph 0142). "The method ... further compris[es] removing the liquid phase of the suspension to form a dry powder of the particles." (See claim 27). "[W]herein the removing of the liquid phase is selected from the group consisting of: evaporation, rotary evaporation, lyophilization, freeze-drying, dia-filitration, centrifugation, force-field fractionation, high-pressure filtration, and reverse osmosis." (See claim 28). For the foregoing reasons the instant method is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaubal et al. (US Patent Application 2004/0245662, Published 12/09/2004, Filed 11/07/2003).

Applicant Claims

A method of producing ultrafine drug particles comprising the steps of: dissolving a drug in a good solvent, mixing the drug suspension in a poor solvent, and subjecting the mixture to high-pressure homogenization. Wherein the mixing occurs such that the poor solvent is circulated into the homogenizer and then the drug-containing solution is added to the circulating solution.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Chaubal et al. is disclosed above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Chaubal et al. does not anticipate the mixing occuring such that the poor solvent is circulated into the homogenizer and then the drug-containing solution is added to the circulating solution. However, Chaubal et al. makes such a step obvious.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to perform the mixing of the two solutions such that the poor solvent is circulated into the homogenizer and then the drug-containing solution is added to the circulating solution. One would have been motivated to do so because Chaubal et al. teach that the mixing and energy addition can be done simultaneously. Therefore, if one wanted to perform the steps in one more efficient way one would have been motivated to do mix and emulsify the solutions with in the homogenizer. For the foregoing

reasons the instant method would have been obvious to one of ordinary skill in the art at the time of the instant invention.

2. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjostrom et al. (International Application Published Under the PCT WO 90/15593, Published 12/27/1990) in view of Bosch et al. (US Patent 5510118, Published 04/23/1996).

Applicant Claims

A method of producing ultrafine drug particles comprising the steps of: dissolving a drug in a good solvent, mixing the drug suspension in a poor solvent, and subjecting the mixture to high-pressure homogenization. Wherein the processing pressure is between 1000 to 6000 psi or 6000 to 20000 psi.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Sjostrom et al. is disclosed above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Sjostrom et al. is silent as to the amount of pressure to be utilized. This deficiency is cured by the teachings of Bosch et al.

Bosch et al. teach, "Process for preparing therapeutic compositions containing nanoparticles." (See title). "In the practice of the present invention the following microfluidizers were used." (See column 6, Lines 58-59). "The premix then can be transferred to the microfluidizer and circulated continuously first at low pressures, then at maximum capacity

having a fluid pressure of from about 3,000 to 30,000 psi until the desired particle size reduction is achieved." (See column 7, Lines 63-67).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Sjostrom et al. with Bosch et al. One would have been motivated to do so because Bosch et al. teach the optimum pressure needed to reduced the particle size to the desired less 1000 nm. For the foregoing reasons the instant method would have been obvious to one of ordinary skill in the art at the time of the instant invention.

3. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjostrom et al. (International Application Published Under the PCT WO 90/15593, Published 12/27/1990) in view of Feldmann (US Patent 2652234, Published 09/15/1953).

Applicant Claims

A method of producing ultrafine drug particles comprising the steps of: dissolving a drug in a good solvent, mixing the drug suspension in a poor solvent, and subjecting the mixture to high-pressure homogenization. Wherein the homogenizer has an online injector.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Sjostrom et al. is disclosed above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Sjostrom et al. does not teach a homogenizer with an online injector. This deficiency is cured by the teachings of Feldmann.

Feldmann teaches, "the matter to be homogenized ... is forced by means of any suitable injector or pump … into the feed channel and through the spiral ducts defined by the rib or ribs." (See column 2, Lines 49-54).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Sjostrom et al. with Feldmann. One would have been motivated to do so because Feldmann teaches that the injector is useful in feeding the solution to homogenized into the mcirofluidizer. For the foregoing reasons the instant method would have been obvious to one of ordinary skill in the art at the time of the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ali Soroush whose telephone number is (571) 272-9925. The examiner can normally be reached on Monday through Thursday 8:30am to 5:00pm E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number For the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available

through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ali Soroush
Patent Examiner
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/Johann R. Richter/

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